MRI CRITERIA TO DIAGNOSE BREAST CANCER

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Abstract:

Contrast enhanced magnetic resonance imaging of the breast offers not only information on cross-sectional morphology of lesions, but provides also information on “functional” criteria like tissue perfusion, capillary permeability, and on tissue signal intensity in T1- and T2-weighted pulse sequences. This article presents the criteria that are useful for the differentiation of (invasive or intraductal) breast cancers and of benign lesions in breast MRI, and provides guidelines for a systematic image analysis. In addition, MR imaging findings in invasive and intraductal cancer as well as benign lesions are presented.

Introduction

In contrast enhanced breast MRI, lesion detection is usually easy due to the cross-sectional image acquisition and the high contrast between the enhancing lesions and the non- or delayed enhancing background. What requires substantial expertise and personal experience, however, is the differentiation of benign and malignant enhancing lesions The detection of an enhancing area (or tumor) is only the start of the process of interpreting a breast MRI study – not its end. In other words: The detection of an enhancing area per se is not sufficient to justify biopsy. Recommending biopsy in every enhancing area would result in an unacceptably low specificity and positive predictive value (1). Therefore, if an enhancing area is identified, every attempt should be made to further classify it. The following paper provides guidelines for image interpretation in contrast enhanced breast MRI (2, 3).

It should be well understood that none of the diagnostic criteria discussed in the following will provide a definite exclusion of malignancy. Moreover, it should always be kept in mind that core biopsy is a safe and cost-effective way to definitively clarify suspicious lesions. With the increasing availability of MR-compatible biopsy systems, this does also hold true for lesions that are visible by breast MRI alone (4,5,6). Last, in each individual case, it will depend on many other contributing factors (patient history, present clinical or radiological findings, and personal concerns of the patient), whether or not, eventually, biopsy is recommended.

Diagnostic criteria for contrast enhanced breast MRI

The diagnostic criteria that are in use for differential diagnosis can be divided into those related to lesion morphology (A), those related to lesion enhancement kinetics (B), and those related to a lesion's signal intensity in *non*-fat-suppressed, non-subtracted pre-contrast T1-weighted and T2-weighted images (C).

Analysis of lesion features according to the MR BI-RADS™ lexicon

When interpreting breast MRI studies, the first step is to determine the *configuration* of a given lesion. It is classified as being a either (i) mass or a (ii) non-mass-like enhancement, or (iii) as a "focus" (2).

A *mass* is a space occupying tumor that has three dimensions. Usually, it has a visible correlate on pre-contrast T1- or T2-weighted images. In fact, the definition of a mass is quite comparable to the term used in mammography.

As opposed to a "mass", *non-mass-like enhancement* means enhancement in an area of the fibroglandular tissue which, on pre-contrast images, appears otherwise normal, i.e. does not exhibit space occupying effects.

A "*Focus*" is defined as a small enhancing area of less than 5 mm which is too small to characterize further. In the vast majority of cases, these "foci" will be due to a focal proliferation of the glandular tissue (so-called focal adenosis). However, it will be impossible to exclude presence of a very small invasive breast cancer or a focus of DCIS or other pathologic entities such as papillomas, small fibroadenoma, a small intramammary lymph node, foreign body granuloma, and so forth. So it is the a-priori probability of breast cancer that has to be weighted in each individual case, and all this should be

taken into account to decide whether short-term follow up, biopsy, or doing nothing is most appropriate to manage solitary or multiple "*Foci*".

While usually, a further classification of a “Focus” is impossible, this is different for “masses” and “non-mass-like enhancement”. These types of lesions are subjected to a further careful analysis of morphology, enhancement kinetics, and signal intensity pattern in T1- and T2-weighted images.

The distinction between “mass like enhancement” and “non-mass-like enhancement” is important because it marks a crossroads for further differential diagnosis. The distinction is comparable, including its diagnostic implications, to the mammographic distinction between a “mass” versus “calcifications alone”, i.e. calcifications without accompanying mass: If a "mass" is identified, the differential diagnosis is usually between a benign versus a malignant solid tumor, i.e. between fibroadenoma and invasive breast cancer. If "non-mass-like enhancement" is present, the differential diagnosis is mainly between intraductal tumor versus benign causes of enhancement without mass effect: mastopathic changes (focal adenosis), hormonal stimulation of normal tissue, inflammatory changes/mastitis, and, rarely, diffusely infiltrating cancer such as invasive lobular cancer.
Accordingly, the decision between “mass” and “non-mass-like enhancement” initiates two separate diagnostic pathways which require different diagnostic criteria for the further distinction of benign and malignant masses or non-mass-like lesions as follows:.

A Analysis of lesion morphology

In “masses”, but not "non-mass-like enhancement", shape and borders are evaluated and described with descriptors that are similar to those used for mammography (with the notable exclusion of the term “obscured” and “indistinct” since MR imaging delivers cross sectional images), and with similar diagnostic implications: Masses with irregular shape are more often malignant than those with round,

oval or lobulated shape. Margins are described as smooth (comparable to a "circumscribed" margin in mammography), irregular or spiculated.. As in mammography, spiculated margins are more suspicious than smooth margins. However, it is important to realize that the accuracy with which margins are assessed depends on the spatial resolution with which the images were acquired. Due to lack of spatial resolution, spiculated masses may appear well-circumscribed. In turn, masses with smooth margins may appear irregular in low spatial resolution images (i.e. images acquired with a pixel size beyond 1 mm) due to partial volume averaging effects (7)

In "*non-mass-like enhancement*", shape and borders are not assessable. Instead, distribution of the non-enhancing areas with the following descriptors: The distribution can follow the ductal system; in this case, it is referred to as being "*segmental*" or "*ductal"*. Just as mammographic calcifications in segmental or ductal distribution, segmental or ductal enhancement in MRI suggests presence of an intraductal pathology, be it a small DCIS or a papilloma (in ductal enhancement) or a large DCIS or peripheral papillomatosis (in segmental enhancement) (13, 14, 15). If the distribution does not follow the ductal system, it is referred to as "*linear*", (a line that does not follow a duct), a "*focal area*" (i.e. non-mass-like enhancement of less than one quarter of a quadrant), "*regional enhancement*" (geographic enhancement of a larger area), "*enhancement in multiple regions*" or "*diffuse enhancement*", i.e. confluent enhancement of more or less the entire breast. The finding of multiple regions or diffuse enhancement has about the same diagnostic implication as a mammogram with diffuse or scattered calcifications: Probability is high that all calcification (in MRI: all enhancement) is due to microcystic blunt duct disease (in MRI: adenosis), however, it is impossible to definitively tell whether any given small calcification (in MRI: area of enhancement) may be due to DCIS or a small invasive cancer. A region of enhancement is more often caused by benign changes than by malignant lesions (16, 17).

If an MRI study covers both breasts (which is highly desirable and will be the case in all axial dynamic contrast enhanced techniques), it is possible to compare both breasts and decide whether a non-mass enhancing area is symmetric or not. Obviously, bilateral symmetric non-mass-like enhancement in any distribution is more often caused by benign changes than by malignant lesions. Accordingly, side-by-side comparisons in bilateral studies are very helpful to deal with the most frequent cause of benign non-mass-like enhancement, i.e. adenosis (ductal or lobular hyperplasia), or hormonal stimulation.

The assessment of shape, margins and configuration offers diagnostic information that is comparable (including the respective diagnostic implication) to the diagnostic information provided by mammography – with the major advantage of breast MRI regarding its cross-sectional acquisition mode which allows a more reliable assessment of shape and margins due to the lack of superimposed normal fibroglandular tissue.

However in addition, as an "add-on" compared with mammography and breast ultrasound, lesion internal enhancement (“lesion internal architecture”) is amenable to assessment. In fact, some of the most powerful diagnostic criteria for the differentiation of benign and malignant tumors belong to this category. Internal enhancement can be described as homogeneous, heterogeneous, or affect only the periphery of a lesion (“rim enhancement”). Last, bright (enhancing) or dark internal septations may be identified (8,9,10,11,12). While homogeneous enhancement is usually found in benign masses, rim enhancement or enhancing internal septations are highly suggestive of malignancy. In turn, dark septations (if present within a lobular or oval mass) are typical of fibroadenomas. Heterogeneous enhancement can be seen both, in invasive breast cancers and in partly sclerotic fibroadenomas.

Internal enhancement in areas of “non-mass-like enhancement” is described as being homogeneous, heterogeneous, stippled or clumped. Although virtually all causes of non-mass-like enhancement

(hormonal stimulation of normal breast tissue, adenosis, inflammation/mastitis, DCIS, diffusely infiltrating cancer such as lobular cancer) can exhibit all types of internal enhancement, there is evidence that a “clumped” and “stippled” internal enhancement is more suggestive of DCIS rather than of a benign non-mass-like enhancement. The predictive value of these features is, however, much lower than that offered by the finding of "***dark internal septations***" or "***rim enhancement***" in masses.

B. Kinetic curve assessment

Both, masses and “non-mass-like enhancement”, but not a “focus”, should be further assessed by a kinetic analysis. In the kinetic analysis, we look at how fast a signal intensity increase appears in a lesion after contrast injection (“***early rise***” or “***wash in rates***”), how strong the signal intensity increase is with respect to baseline (pre-contrast) lesion signal intensity, and what happens with the signal after the early post-contrast phase (“***delayed phase enhancement***”). To evaluate kinetics, a small Region of Interest (ROI) is placed selectively in the part of an enhancing area that appears brightest on the first post-contrast image. Although CAD software may facilitate this by color-coding the degree or type of enhancement in a given lesion and may assist in interpreting breast MRI studies, CAD users may be tempted to overemphasize kinetic aspects of breast MRI differential diagnosis by simply calling all areas marked by the CAD system – and disregarding others which are not marked. Moreover, CAD systems tend to use a fixed "enhancement threshold" or "wash out threshold" for differential diagnosis of enhancing lesions – which is clearly inappropriate (see below).

Early rise

The rationale of calculating enhancement rates is based on the observation that malignant lesions tend to have higher wash in rates than benign ones. And in fact, the vast majority of invasive breast cancers exhibits fast, strong enhancement that peaks already in the early post-contrast phase. This is also intuitively used by radiologists who do not use "kinetics" for lesion differential diagnosis. Also in non-

dynamic, purely morphologic interpretation models for reading breast MRI studies, a lesion appears more conspicuous if it exhibits a very bright post-contrast signal – which is the same as "strong and rapid wash in".

“Wash in rates” can be quantified and given in percent signal intensity increase. To account for differences in baseline tissue T1 relaxation times, enhancement is calculated as signal intensity increase relative to baseline values (18,19):

$$\frac{(SI_{post} - SI_{pre})}{SI_{pre}} \times 100 \ [\%]$$

where SI_{pre} is baseline signal intensity, and SI_{post} is signal intensity after i.v. gadolinium chelate injection. Relative signal intensity increase that occurs in a certain period of time – usually the first post-contrast minute – is referred to as "enhancement rate" (e.g., "80% per minute"). We distinguish “*slow*”, “*medium*”, and “*rapid*” early rise. There is no universally applicable definition as to what constitutes exactly “slow” versus “medium” or “rapid” early enhancement – this has to be defined individually for each set up. The reason is that quantitative enhancement rates may vary with different types of pulse sequences, contrast agent injection modes, site of venous injection, heart rate, and types of equipment. In our set up (1.5T system, 2D gradient echo, TR/TE/FA 290/4.6/90°, 0.1 mmol/kg Gd-DTPA as bolus via an 18G venous line, followed by 20 cc saline flush), a wash in rate of more than 80% represents fast enhancement; 30% signal intensity increase is referred to as slow enhancement.

Although rapid wash in the early post-contrast phase is found in the vast majority (about 80%) of invasive cancers, slowly enhancing invasive cancers do exist; mainly, they belong to the lobular type, or exhibit an abundant desmoplastic activity. Therefore, if one uses a threshold in order to classify lesions based on their enhancement rates, one runs the risk of missing these cancers. In addition, many benign lesions exhibit rapid enhancement, such that the use of an "enhancement threshold" will cause a

high number of false positive findings as well.

The use of an “enhancement threshold” to diagnose breast cancer had been proposed back in the 1990ies, when dynamic contrast-enhanced breast MRI offered such a poor spatial resolution that a meaningful analysis of morphologic details was impossible (18). Since then, MR technology has improved, such that it is possible to obtain both, high spatial resolution and a dynamic, fast acquisition, in order to evaluate both, lesion enhancement kinetics and lesion morphology. With high spatial and high temporal resolution, criteria for differential diagnosis have been developed that offer a much better differentiation of benign and malignant lesions than what is offered by using an "enhancement threshold" alone. With the increasing availability of breast MRI CAD systems, it seems that the idea of an “enhancement threshold” celebrates merry resurrection again. This should be discouraged – reducing breast MRI differential diagnosis to a binary decision (beyond or below threshold) is an unacceptably limited approach which will cause both, unnecessary false positive and false negative diagnoses. In addition, it is unacceptable because enhancement thresholds will depend on many confounding factors and may therefore not be simply copied from one institution to another.

Delayed phase enhancement

After the early rise, the further time course of signal intensity is usually assessed visually by looking at the time/signal intensity curves. We distinguish 3 different types: Persistent enhancement (curve exhibits steady signal intensity increase), plateau (fast early upstroke, followed by a plateau after the 3rd post contrast minute), or wash out (fast early upstroke followed by a loss of signal intensity after the 3rd post contrast minute). The rationale for assessing curve shape is that a persistent time course is indicative of a benign lesion, whereas a wash-out time course supports the diagnosis of a malignant lesion (19). A plateau time course may be found both in benign and malignant lesions.

The curve type analysis is done complementary to the morphologic analysis, and is mostly useful for differential diagnosis of masses that exhibit rapid enhancement. Lesion with medium or slow early rise, i.e. lesions with only moderate or poor angiogenic activitiy, will usually always exhibit a persistent time course, such that the absence of a wash out in a lesion with slow enhancement cannot be used as a sign of benignity.

C. Analysis of lesion signal intensity in pre-contrast T1 weighted and in T2-weighted TSE images

In all other clinical applications of MR imaging, a careful analysis of lesion signal intensity in T1- and T2-weighted images are used to classify imaging findings. This should also hold true for breast MR imaging – and yet this is greatly ignored in many papers that deal with differential diagnosis in breast MRI. This is very unfortunate because the wealth of diagnostic information inherent to non-fat-suppressed pre-contrast images is intriguing and can be used for further differential diagnosis of fat necrosis, intramammary lymph nodes, inflammatory cysts, and for the distinction of fibroadenomas and breast cancers. Accordingly, in addition to morphological and kinetic features, a lesion's signal intensity in ***non***-fat-suppressed T2-weighted images and in T1-weighted ***pre***-contrast ***non***-fat-suppressed images should always be assessed (20).

If on ***non***-fat-suppressed, ***pre-contrast*** T1-weighted images, bright signal is seen within a lesion, this is a strong evidence for a benign finding. If in a ***non***-fat-suppressed ***pre-contrast*** T1-weighted image a space-occupying mass appears isointense compared to the adjacent fibroglandular tissue, this should raise the suspicion of breast cancer. If in the same pulse sequence a mass exhibits a low signal intensity compared with normal adjacent tissue, this is more suggestive of fibroadenomas.

In addition to the T1-weighted dynamic contrast enhanced series, high spatial resolution non-fat-

suppressed T2-weighted Turbo Spin or Fast Spin Echo (TSE, FSE) images are acquired with an anatomic position that exactly matches with that of the dynamic T1-weighted series. By doing so, an accurate comparison of a lesion's signal intensity in T1-weighted pre- and post-contrast images and its signal intensity in non-fat-suppressed, T2-weighted images becomes feasible. Bengin masses such as fibroadenomas or intramammary lymph nodes usually exhibit a hyperintense signal compared with the normal fibroglandular tissue. The typical dark internal septations of myxoid fibroadenomas (see below) are sometimes even best visualized in T2-weighted TSE images against the bright myxoid stroma. The majority of breast cancers exhibit an iso- or hypointense signal compared with regular fibroglandular tissue. This is with the notable exception of mucinous and medullar cancer. Fatty tissue signal (bright on T2- and on T1-weighted images) within an enhancing mass is clearly indicative of a benign mass (intramammary lymph node with fatty hilum, fresh fat necrosis).

MR imaging findings in benign and malignant breast lesions

Invasive breast cancers

The typical invasive breast cancer appears as a mass with irregular shape and with irregular or spiculated margins. Internal enhancement is heterogeneous or shows rim enhancement. At kinetic analysis, the "typical" invasive cancer will exhibit rapid and strong enhancement, followed by a wash-out in the early post-contrast phase. In T1-weighted pre-contrast images and on non-fat-suppressed T2-weighted images, the "typical" invasive breast cancer will exhibit low signal intensity, equivalent to or lower than that of the normal fibroglandular tissue. Lobular invasive cancer may not form masses, but exhibit an "Indian path" growth pattern; in theses cases, non-mass-like enhancement may be present. Since angiogenic activity of diffusely growing lobular invasive cancer may be lower than that found in solid invasive breast cancers, enhancement of lobular invasive cancer may be slow (21, 22)

Intraductal cancers (ductal carcinoma in-situ, "DCIS")

The great majority of DCIS do not appear as masses. Instead, non-mass-like enhancement that follows the ductal system is the hallmark of DCIS in breast MRI. Non-mass-like enhancement with asymmetric, i.e. unilateral, ductal or segmental distribution is in at least 30% of cases due to DCIS; in other words: This finding has a high PPV for intraductal cancer. Since breast MRI is able to demonstrate DCIS that does not exhibit calcifications on mammography, ductal or segmental enhancement should entail biopsy. If an intraductal cancer is sufficiently large, internal enhancement can be evaluated. It is almost always heterogeneous, exhibiting an enhancement pattern that has been referred to as being "granular", "stippled" or "clumped".

Fibroadenomas

Fibroadenomas appear as masses, almost always with roundish, oval, or lobular shape, and with smooth margins. Myxoid fibroadenomas exhibit fast enhancement with persistent time course. On T2-weighted non-fat-suppressed images, myxoid fibroadenomas exhibit a high signal intensity compared with the adjacent fibroglandular tissue (yet not as high as fatty tissue or cysts). This is in contrast to the majority of invasive breast cancers that tend to exhibit low signal intensity (isointense to fibroglandular tissue) on non-fat-suppressed T2-weighted TSE images. Internal enhancement of myxoid fibroadenomas is either homogeneous, or dark internal septations are visible. Dark internal septations offer a very high negative predictive value for breast cancer. Sclerotic fibroadenomas exhibit only weak enhancement or no enhancement at all. Therefore, they may be missed if only subtracted or fat-suppressed post-contrast images are evaluated. Dark internal septations are usually not perceivable because the entire lesion is isointense to the signal of the septa in all pulse sequences.

Nodular mastopathic changes, focal adenosis

So-called nodular-mastopathic changes and focal adenosis are a notorious cause of diagnostic

difficulties. They appear as more or less bilateral symmetric multiple foci or diffuse or regional non-mass-like enhancement that affects both breasts. Kinetic features are usually not helpful to clarify, because many of these foci exhibit fast, strong, early enhancement and even a wash out time course. Just as in mammography in patients with sclerosing adenosis or blunt duct disease, where it is impossible to exclude that one of the calcifications is due to DCIS or a very small invasive cancer, it is impossible to exclude presence of breast cancer in each of the small enhancing foci. If the entire parenchyma exhibits diffuse or multifocal, early enhancement, we call this an “MR-mammographically dense breast” to communicate that sensitivity of the given breast MRI study may be greatly reduced, because enhancing cancer can be masked by enhancing fibroglandular tissue.

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